Wnt7a regulates multiple steps of neurogenesis.

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Public Summary:

The signaling protein Wnt7a has been implicated in ensuring nerve cells called neurons reach their correct targets and in the formation of synapses between neurons; however studies of the role of Wnt7a in the early steps of neurogenesis have just begun. Using a mouse model, we found that Wnt7a is essential for perpetuating the self-renewal of neural stem cells in the brain and for converting and maturing these stem cells into neurons. Genetically engineered mice in which the Wnt7a gene had been deleted had substantially fewer neural stem cells than did mice that still expressed the Wnt7a gene. Further, loss of Wnt7a increased the rate of cell cycle exit in neural progenitor cells in the hippocampus, a region of the brain important for learning and memory. Loss of Wnt7a expression also led to a substantial decrease in the number of newborn neurons in this region, as well as impaired development and growth of these neurons. We also found that Wnt7a regulated neural stem cell proliferation and differentiation by activating cell signaling pathways controlled by a protein known as beta-catenin. Wnt7a exercises critical control over multiple steps of neurogenesis by regulating genes involved in both cell cycle control and neuronal differentiation. Further, this study suggests that modulation of Wnt7a expression could provide a means to improve learning and memory.

Scientific Abstract:

Although Wnt7a has been implicated in axon guidance and synapse formation, investigations of its role in the early steps of neurogenesis have just begun. We show here that Wnt7a is essential for neural stem cell self-renewal and neural progenitor cell cycle progression in adult mouse brains. Loss of Wnt7a expression dramatically reduced the neural stem cell population and increased the rate of cell cycle exit in neural progenitors in the hippocampal dentate gyrus of adult mice. Furthermore, Wnt7a is important for neuronal differentiation and maturation. Loss of Wnt7a expression led to a substantial decrease in the number of newborn neurons in the hippocampal dentate gyrus. Wnt7a(-/-) dentate granule neurons exhibited dramatically impaired dendritic development. Moreover, Wnt7a activated beta-catenin and its downstream target genes to regulate neural stem cell proliferation and differentiation. Wnt7a stimulated neural stem cell proliferation by activating the beta-catenin-cyclin D1 pathway and promoted neuronal differentiation and maturation by inducing the beta-catenin-neurogenin 2 pathway. Thus, Wnt7a exercised critical control over multiple steps of neurogenesis by regulating genes involved in both cell cycle control and neuronal differentiation.